

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 140 to about 310 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of~~ the parasite *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that

at least five amino acid residues are present of the amino acid residue sequence from position 136 through 149, when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

2. (Original) The recombinant HBc chimer protein molecule according to claim 1 present as self-assembled particles.

3. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein said B cell epitope consists essentially of two to about five repeats of a 4 to about 11 amino acid residue sequence.

4, 5. Cancelled.

6. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein Domain I consists essentially of the HBc sequence from position 1 through position 75.

7. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein Domain II independently includes zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

8. (Original) The recombinant HBc chimer protein molecule according to claim 1 wherein said sequence heterologous to HBc at position 150 to the C-terminus of Domain IV comprises an amino acid residue sequence that constitutes a T cell epitope of the same species of *Plasmodium* as said B cell epitope.

9. (Currently Amended) A recombinant hepatitis B virus core (HBc) protein chimer molecule with a sequence of about 155 to about 235 amino acid residues that contains four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through 75 of HBc;

(b) Domain II is about 18 to about 46 residues in length of which (i) 10 residues are present in a sequence of HBc at positions 76 to 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or Plasmodium vivax~~ that is peptide-bonded between the residues of positions 78 and 79, said B cell epitope being comprised of two to about five repeats of an amino acid residue sequence, said Domain independently including zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of~~ comprises the HBc sequence from position 86 through position 135; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) ~~zero~~ one to

three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 50 amino acid residues in a sequence that constitutes a T cell epitope of *Plasmodium falciparum* ~~the same species of *Plasmodium* as said B cell epitope~~ peptide-bonded to the final HBc amino acid residue present in the chimera, and wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

10. (Original) The recombinant HBc chimera protein molecule according to claim 9 wherein Domain IV comprises one amino acid residue to a sequence of about nine amino acid residues of the HBc sequence from residue position 141 through about position 149 peptide-bonded to residue 140.

11. (Original) The recombinant HBc chimera protein molecule according to claim 10 wherein Domain IV consists essentially of a sequence of nine amino acid residues of the HBc sequence from residue position 141 through position 149 peptide-bonded to residue 140.

12. Cancelled.

13. (Original) The recombinant HBc chimera protein molecule according to claim 9 wherein the repeated sequence of said B cell epitope of Domain II is Asn-Ala-Asn-Pro.

14. (Original) The recombinant HBc chimera protein molecule according to claim 13 wherein the repeated sequence of

said B cell epitope of Domain II is repeated three or four times.

15. (Original) The recombinant HBc chimer protein molecule according to claim 14 wherein the repeated sequences are peptide-bonded to each other without interruption.

16. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 15 wherein said B cell epitope includes a second CS protein sequence from ~~the same~~ *Plasmodium falciparum* species that is peptide-bonded to said repeated sequence.

17. (Original) The recombinant HBc chimer protein molecule according to claim 16 wherein said second CS protein sequence is Asn-Val-Asp-Pro.

18. Cancelled.

19. (Original) The recombinant HBc chimer protein molecule according to claim 17 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

20. (Original) The recombinant HBc chimer protein molecule according to claim 16 wherein said second CS protein sequence is SEQ ID NO:126 (Asn-Ala-Asn-Pro-Asn-Val-Asp-Pro).

21. Cancelled.

22. (Original) The recombinant HBc chimer protein molecule according to claim 20 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

23. (Currently Amended) The recombinant HBc chimer protein molecule according to claim 10 wherein said one to three cysteine residues are present in Domain IV within about 30 residues of the carboxy-terminus of the chimeric molecule.

24. (Original) The recombinant HBc chimer protein molecule according to claim 23 wherein said one to three cysteine residues are present in said T cell epitope.

25. (Original) The recombinant HBc chimer protein molecule according to claim 24 wherein said T cell epitope is present and has the sequence of SEQ ID NO: 148 or 25 (EYLNKIQNLSLSTEWSPCSVT OR YLDKVRATVGTEWTPCSVT).

26. (Original) The recombinant HBc chimer protein molecule according to claim 9 present as self-assembled particles.

27. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 155 to about 235 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of~~ the parasite *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III, and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, ~~(ii) zero to three cysteine residues,~~ (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 50 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus ~~with the proviso that at least five amino acid residues are present of the HBc amino acid residue sequence from position 136 through 149 when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present,~~ and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

28. (Original) The particles according to claim 27 whose HBc chimer protein molecules have a sequence length of about 165 to about 210 amino acid residues.

29. (Original) The particles according to claim 27 wherein said B cell epitope consists essentially of two to about five repeats of a 4 to about 11 amino acid residue sequence.

30, 31. Cancelled.

32. (Original) The particles according to claim 27 wherein Domain I consists essentially of the HBc sequence from position 1 through position 75.

33. (Original) The particles according to claim 27 wherein Domain II independently includes zero to three peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

34. (Currently Amended) The particles according to claim 27 wherein said sequence heterologous to HBc at position 150 to the C-terminus of Domain IV comprises an amino acid residue sequence that constitutes a T cell epitope of Plasmodium falciparum ~~the same species of Plasmodium as said B cell~~ epitope.



35. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or Plasmodium vivax~~ that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being comprised of two to about five repeats of an amino acid residue sequence, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises the HBc sequence of residues 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 140 through 149 peptide-bonded to the residue of position 140, (ii) ~~zero~~ one to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 25 amino

acid residues in a sequence that constitutes a T cell epitope of the same species of *Plasmodium* as said B cell epitope, said T cell epitope sequence being peptide-bonded to the final HBc amino acid residue present in a chimer molecule or a cysteine residue, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

36. (Currently Amended) The particles according to claim 35 wherein Domain IV comprises one to a sequence of nine amino acid residues of the HBc sequence from residue position 141 through position 149 linked between residue 140 of said Domain III sequence and a *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ T cell epitope.

37. (Original) The particles according to claim 36 wherein the nine amino acid residues of the HBc sequence from residue position 141 through position 149 are present.

38. Cancelled.

39. (Original) The particles according to claim 35 wherein the repeated sequence of said B cell epitope of Domain II is Asn-Ala-Asn-Pro.

40. (Original) The particles according to claim 39 wherein the repeated sequence of said B cell epitope of Domain II is repeated three or four times.

41. (Original) The particles according to claim 40 wherein the repeated sequences are peptide-bonded to each other without interruption.

42. (Currently Amended) The particles according to claim 41 wherein said B cell epitope includes a second CS protein sequence from Plasmodium falciparum ~~the same Plasmodium species~~ that is peptide-bonded to said repeated sequence.

43. (Original) The particles according to claim 42 wherein said second CS protein sequence is Asn-Val-Asp-Pro.

44. Cancelled.

45. (Original) The particles according to claim 43 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

46. (Original) The particles according to claim 42 wherein said second CS protein sequence is SEQ ID NO:126 (Asn-Ala-Asn-Pro-Asn-Val-Asp-Pro).

47. Cancelled.

48. (Original) The particles according to claim 46 wherein said second CS protein sequence is peptide-bonded at the amino-terminus of said repeated sequence.

49. (Original) The particles according to claim 35 wherein said B cell epitope of *Plasmodium falciparum* has an

amino acid residue sequence selected from the group consisting of SEQ ID NOS:1-14.

50. Cancelled.

51. (Original) The particles according to claim 35 wherein said T cell epitope of *Plasmodium falciparum* is present and has the amino acid residue sequence of SEQ ID NO:24.

52. Cancelled.

53. (Currently Amended) The particles according to claim 36 ~~further including~~ wherein said one to three cysteine residues in the Domain IV sequence are present within about 30 residues of the carboxy-terminus of the chimeric molecule.

54. (Original) The particles according to claim 53 having one cysteine residue in the Domain IV sequence.

55. Cancelled.

56. (Currently Amended) Particles comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contain four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence that constitutes a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or Plasmodium vivax~~ is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being selected from the group consisting of SEQ ID NOs:1-21, said Domain II including two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide bonded to residue 85; and

(d) Domain IV comprises the sequence of HBc residues 136-140 peptide-bonded to residue 135 plus one to nine residues of a HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 140 and also peptide-bonded to a *Plasmodium falciparum* ~~or Plasmodium vivax~~-T cell epitope of a sequence of up to about 25 amino acid residues that includes a cysteine residue, and

wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

57. (Currently Amended) The particles according to claim 56 wherein Domain IV comprises nine amino acid residues of the HBc sequence from residue position 141 through position 149 bonded between said residue 140 and said *Plasmodium falciparum* ~~or Plasmodium vivax~~-T cell epitope.

58. (Original) The particles according to claim 57 wherein said B cell epitope is of the CS protein of *Plasmodium falciparum* that is selected from the group consisting of SEQ ID NOs:1-14 and said *Plasmodium falciparum* T cell epitope has the amino acid sequence of SEQ ID NO:24.

59. Cancelled.

60. (Currently Amended) A vaccine or inoculum comprising an immunogenic effective amount immunogenic particles dissolved or dispersed in a pharmaceutically acceptable diluent, wherein said immunogenic particles are comprised of a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules having a length of about 140 to about 310 amino acid residues that contain four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises the HBc sequence from position 1 through position 75 or comprises a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc;

(b) Domain II comprises about 18 to about 58 amino acid residues peptide-bonded to residue 75 of which (i) a sequence of HBc is present from HBc positions 76 through 85 and (ii) a sequence of 8 to about 48 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of ~~a species of the parasite~~ *Plasmodium falciparum* that is peptide-bonded between the HBc residues of positions 78 and 79;

(c) Domain III is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises a sequence of HBc from residue 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) zero to nine residues of a HBc amino acid residue sequence from position 141 through 149, (ii) zero to three cysteine residues, ~~(ii) zero to three cysteine residues,~~ (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) up to 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, ~~with the proviso that at least five amino acid residues are present of the amino acid residue sequence from position 136 through 149, when (a) zero cysteine residues are present and (b) fewer than about five heterologous amino acid residues are present, and~~  
wherein no more than 10 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

61. (Currently Amended) The vaccine or inoculum according to claim 60 wherein said immunogenic particles are those having a sequence of about 165 to about 210 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76

through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being comprised of two to about five repeats of an amino acid residue sequence, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide-bonded to residue 85; and

(d) Domain IV comprises the HBc sequence of residues 136 through 140 peptide-bonded to the residue of position 135 of Domain III and (i) nine residues of a HBc amino acid residue sequence from position 141 through 149 peptide-bonded to the residue of position 140, (ii) one to three cysteine residues, (iii) fewer than three arginine or lysine residues, or mixtures thereof adjacent to each other, and (iv) a *Plasmodium falciparum* ~~or *Plasmodium vivax*~~ T cell epitope, said T cell epitope sequence being peptide-bonded to the final HBc amino acid residue present in a chimer molecule or a cysteine residue, and

wherein no more than 5 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

62. (Previously Presented) The vaccine or inoculum according to claim 60 wherein Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from



position 76 through 85 and (ii) a sequence of 8 to about 36 residues that constitute a B cell epitope of the circumsporozoite (CS) protein of *Plasmodium falciparum* that is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being comprised of three or four repeats of an amino acid residue sequence Asn-Ala-Asn-Pro, said Domain independently including zero to two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope.

63. (Currently Amended) The vaccine or inoculum according to claim 62 wherein the repeated sequences are peptide-bonded to each other without interruption and wherein said B cell epitope includes a second CS protein sequence from *Plasmodium falciparum* ~~the same *Plasmodium* species~~ that is peptide-bonded to said repeated sequence.

64. (Currently Amended) The vaccine or inoculum according to claim 60 wherein said immunogenic particles are those comprised of recombinant hepatitis B virus core (HBc) protein chimer molecules, said molecules having a sequence of about 165 to about 210 amino acid residues that contain four peptide-linked domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I ~~consists essentially of~~ comprises a sequence of residues 1 through position 75 of HBc;

(b) Domain II comprises about 18 to about 46 amino acid residues peptide-bonded to residue 75 of which (i) 10 residues are present in a sequence of HBc from position 76 through 85 and (ii) a sequence that constitutes a B cell epitope

of the circumsporozoite (CS) protein of *Plasmodium falciparum* or ~~*Plasmodium vivax*~~ is peptide-bonded between the residues of HBc positions 78 and 79, said B cell epitope being selected from the group consisting of SEQ ID NOs:1-21, said Domain II including two peptide-bonded residues on either side of said B cell epitope that are other than those of HBc or said B cell epitope;

(c) Domain III ~~consists essentially of the~~ is an HBc sequence from position 86 through position 135 peptide bonded to residue 85; and

(d) Domain IV comprises the sequence of HBc residues 136-140 peptide-bonded to residue 135 plus nine residues of a HBc amino acid residue sequence from position\_141 through 149 peptide-bonded to the residue of position 140 and also peptide-bonded to a *Plasmodium falciparum* T cell epitope of a sequence of up to about 25 amino acid residues that includes a cysteine residue, and

wherein no more than 5 percent of the HBc amino acid residues are substituted as compared to SEQ ID NO:170 from position 1 through 149.

65. (Previously Presented) The vaccine or inoculum according to claim 64 wherein said immunogenic particles are those wherein said B cell epitope is of the CS protein of *Plasmodium falciparum* that is selected from the group consisting of SEQ ID NOs:1-14 and said *Plasmodium falciparum* T cell epitope has the amino acid sequence of SEQ ID NO:24.

66. Cancelled.

67. (Original) The vaccine or inoculum according to claim 60 that is adapted for parenteral administration.

68-75. Cancelled.